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The safety or risk of antihistamine use in pregnancy: reassuring data are helpful but not sufficient

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Antihistamines are some of the most frequently used medications in early pregnancy, with several indications for use including use that might increase during pregnancy such as for the treatment of nausea and vomiting.(1–3) In this issue of JACI: In Practice, Li et al. evaluated 16 previously reported associations between specific antihistamines and specific types of birth defects, and also conducted an exploratory analysis of all other specific antihistamine-defect combinations.(4) In most cases, a single study will not provide definitive information on the safety or risk of medication exposures, particularly since randomized trials of medication exposures in pregnancy are usually not possible. The epidemiological approach used by Li et al. builds on prior knowledge and reconsiders it in light of new data, and has the potential to inform our understanding of the safety or risk of specific medications more so than a single study. By specifically addressing the previously reported associations, the new analyses will either confirm or refute the earlier findings; confirmation of formerly noted associations by an independent data source strengthens evidence that the positive effect estimate represents a true biological event and makes it far less likely that it is a chance finding. One of the greatest limitations of studies of medications in pregnancy is the potential for chance findings of positive associations, and the difficulty in separating chance from true effects. Statistical techniques to address the issue of multiple comparisons are equally likely to suppress true findings and chance findings, as the statistical approach cannot make this distinction, but the approach employed by Li et al. is a step in the correct direction towards maximizing the identification of true positive associations.

The group of antihistamines considered by Li et al. includes both prescription and over-the-counter medications which is important because many commonly used antihistamines have moved from prescription to over-the-counter status in the past decade and use has presumably increased with this shift. For example, loratadine moved to over-the-counter availability in December 2002, and prevalence of use during pregnancy increased from just

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over 2% in 1998–1999 to nearly 5% in 2008–2009.(5) Over the entire time period, Li et al. report that nearly 14% of control mothers self-reported use of at least one antihistamine during the first trimester. With about 4 million births per year in the U.S., this would mean over half a million babies born each year are exposed to antihistamines in utero early in pregnancy, if the prevalence of use across the U.S. is similar to that of participants in the Slone Epidemiology Center's Birth Defects Study.

Despite the frequency of use for many medications, including antihistamines, during pregnancy, we continue to avoid the use of the term "safe" in most situations given the inadequate level of knowledge about fetal impact. The widespread dissemination and use of "safe" medication lists for use in pregnancy suggests that there is demand for a listing of what is safe, but ignores the lack of data on many adverse outcomes that might occur and avoids a careful evaluation of the need for a medication.(6) Inclusion of a medication on a "safe" list for use in pregnancy suggests that there are no concerns about potential adverse effects on the fetus, and might encourage use in situations for which there could be suitable non-pharmacologic management strategies. And, women might use a "safe" list in place of a more informed conversation with their health care provider. It is important that women do not stop or start a medication during pregnancy without first discussing the risks and benefits with their health care provider. For some conditions, the risks to both the mother and fetus might actually increase with treatment cessation. This informed conversation will also address the potential combined impact of all medications needed to manage all health conditions of that woman, a factor that is pertinent to antihistamine use given the association with use of a number of other medications such as corticosteroids and antibiotics.(4)

While the findings of Li et al. and previous analyses are in general reassuring and suggest that antihistamine exposures are unlikely to be strongly associated with any of the more common major birth defects, the question of safety for use in pregnancy remains.(4, 7, 8) While lack of strong associations with major birth defects is very helpful information for women who have been inadvertently exposed and then recognize their pregnancy, it is not sufficient to change recommendations about what should be used during a pregnancy for a range of indications treated with antihistamines. While birth defects are an important adverse pregnancy outcome and have major implications for medical care needs, costs, and potentially have lifelong consequences, they are not the only adverse outcome that might result from medication exposure during pregnancy. In addition to major birth defects, medication use in pregnancy might impact the risk of spontaneous abortion, preterm birth, fetal growth and development, and neurocognitive development.(9–11) If a medication increases the risk of spontaneous abortion, then a finding of no association between the medication and adverse outcomes among the live births might not indicate safety but might instead indicate selective loss of exposed fetuses. Exposure to valproic acid in pregnancy is associated with an increased risk of some birth defects including spina bifida and cleft palate, but an association has also been suggested for neurodevelopmental delay and autism. (10, 11) And while data are very limited for understanding the potential risk of major birth defects associated with most medications used in pregnancy, the data are much scarcer for the other potential adverse outcomes. For example, there are very few data available to evaluate potential associations between medication exposures during pregnancy and neurodevelopmental delay in offspring, in part because of the necessity for either

longitudinally linked data or several years of follow-up since diagnoses typically occur during early or mid-childhood.

While some use of antihistamines might occur after planning and consideration of the potential risk and benefits, particularly for treatment of nausea and vomiting of pregnancy, there is likely much inadvertent exposure to antihistamines that occurs prior to pregnancy recognition. However, in the ideal situation of planning a pregnancy and having a discussion in advance of pregnancy about medication options during pregnancy, one key factor is an assessment of the need for medication during pregnancy. The need for medication will be influenced by severity of the maternal condition and by the likely impact of non-treatment or delayed treatment on both the fetus and the mother. For example, lack of appropriate treatment for pregnant women with epilepsy that results in seizures can increase the risk of injury and death for the woman and potentially also harm the fetus.(12) And, while non-treatment during pregnancy is typically not an option for epilepsy, the specific treatment selected and the dose can be considered in a manner to minimize the risk to the fetus. Once need has been established, the conversation shifts to treatment options with the goal of effectively treating the maternal condition while minimizing the risk to the fetus. For conditions commonly treated with antihistamines, an evaluation of need for treatment will likely be based at least in part on the severity and duration of symptoms experienced.

The intentional use of medication in pregnancy, including the use of antihistamines, should only occur in the context of a thoughtful evaluation of the risk versus the benefit for a woman given the full context of her medical profile and need. Women and their health care providers should discuss the available options, and when data are available to inform the relative safety or risk, choose the safest option and lowest effective dose when medication is deemed necessary. The report by Li et al. in this issue makes an important and reassuring contribution of data on the relative safety or risk of antihistamine use in pregnancy, but more robust data on a broader range of outcomes is needed to truly inform safer medication use in pregnancy.(4) In addition, limiting use of medication in pregnancy to situations that require treatment will minimize any unanticipated risk to the fetus while still addressing the needs of the pregnant woman.

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